

Stage-dependent Dynamics of Neuroinflammation across the Alzheimer's Continuum

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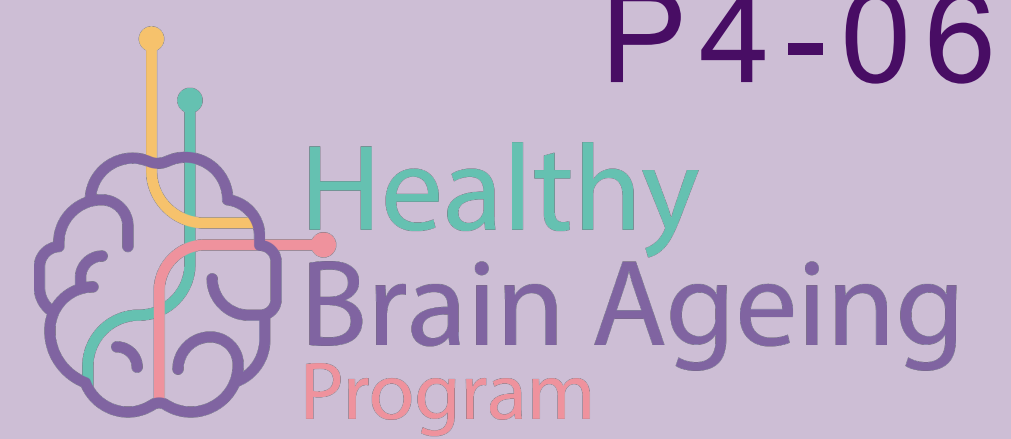
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Highlights

Associations of YKL-40 with AD pathology uncouples and reverses with disease progression
GFAP shows stable links with pathology, with increasingly stronger cognitive associations in later stages
YKL-40 and GFAP capture distinct, evolving astrocytic processes in AD

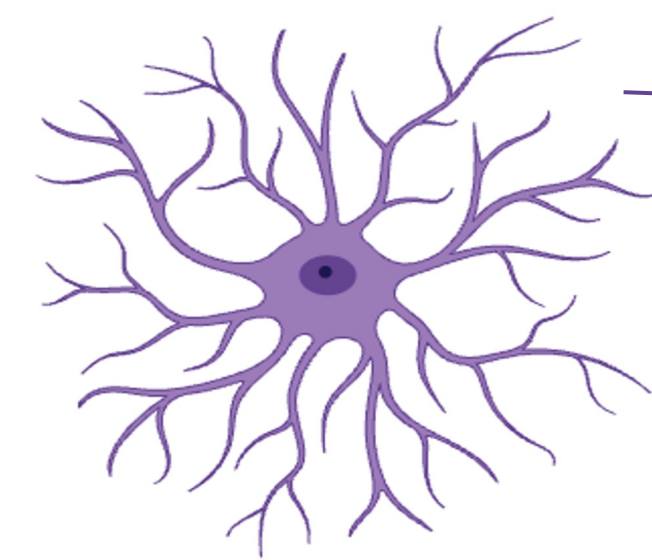


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INTRODUCTION & OBJECTIVES

- **Neuroinflammation** is a core feature of Alzheimer's Disease (AD)
- Glial responses may become progressively **dysregulated** with disease progression
- There is a need to delineate **biomarkers** that may reflect distinct phases of the glial response

GFAP



Reactive astrocyte

YKL-40

- Released during astrogliosis
- Reflects astrocytic cytoskeletal breakdown & injury
- Strong predictor of poorer clinical prognosis & decline
- Involved in extracellular matrix remodelling, tissue repair
- May reflect early compensatory glial responses to emerging pathology

Aims: This study aimed to understand the differential stage-dependent dynamics of GFAP and YKL-40 in relation to AD pathology and cognitive function across the AD continuum

METHODS

- **Total of 420 participants** (Aged ≥ 50) experiencing new-onset cognitive decline recruited from the **Healthy Brain Ageing Clinic (University of Sydney)**
Exclusions: neurological/major psychiatric disease.
 - Healthy Controls (HC; n = 12); Subjective Cognitive Decline (SCD; n = 202); amnesic Mild Cognitive Impairment (aMCI; n = 84); Alzheimer's Disease (AD; n = 16)

- Serum YKL-40 (ELISA); Plasma GFAP, pTau217, A β 42/40 & NfL (Quanterix Simoa HD-X)

➤ **pTau217-positive** (pTau >0.63 pg/mL): **N = 79**

➤ **pTau217-negative** (<0.4 pg/mL): **N = 278**

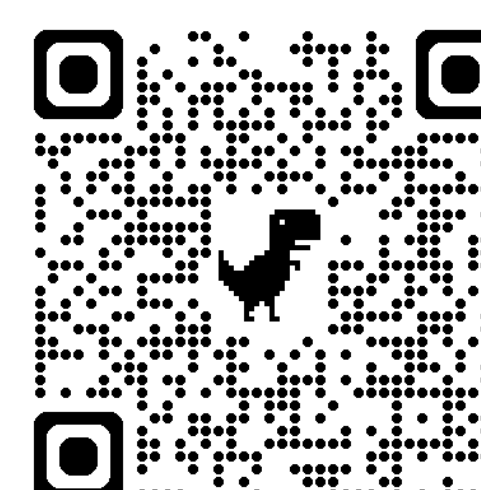
- Standardised neuropsychological assessment; composite scores calculated for each cognitive domain (**Fig 1**)

Fig 1. Neuropsychological tests for each cognitive domain

Verbal Memory	Executive Function	Processing Speed	Global Cognition (Preclinical Alzheimer's Cognitive Composite; PACC)
RAVLT (delayed recall trial 7) Logical Memory II	Trail Making Test B Stroop Condition 3 Stroop Condition 4	Trail Making Test A Stroop Condition 1 Stroop Condition 2	RAVLT (delayed recall trial 7) FAS Verbal Fluency Test Digit Span Logical Memory II

- **Multiple linear regression** conducted glial biomarker (GFAP, YKL-40) x pTau-group interaction terms for AD pathology outcomes (pTau217, A β 42/40, NfL) and cognitive outcome (memory, executive function, processing speed, global cognition) [FDR-corrected; Adjusted for age, sex & eGFR]

- Exploratory analyses conducted by **diagnostic classification**



RESULTS

YKL-40 showed stage-dependent associations with pTau217 across pTau217 group and clinical diagnosis (Fig 2 & 3)

- pTau217-negative: $r = 0.208$, $p < .001$
- pTau217-positive: $r = -0.251$, $p = .025$

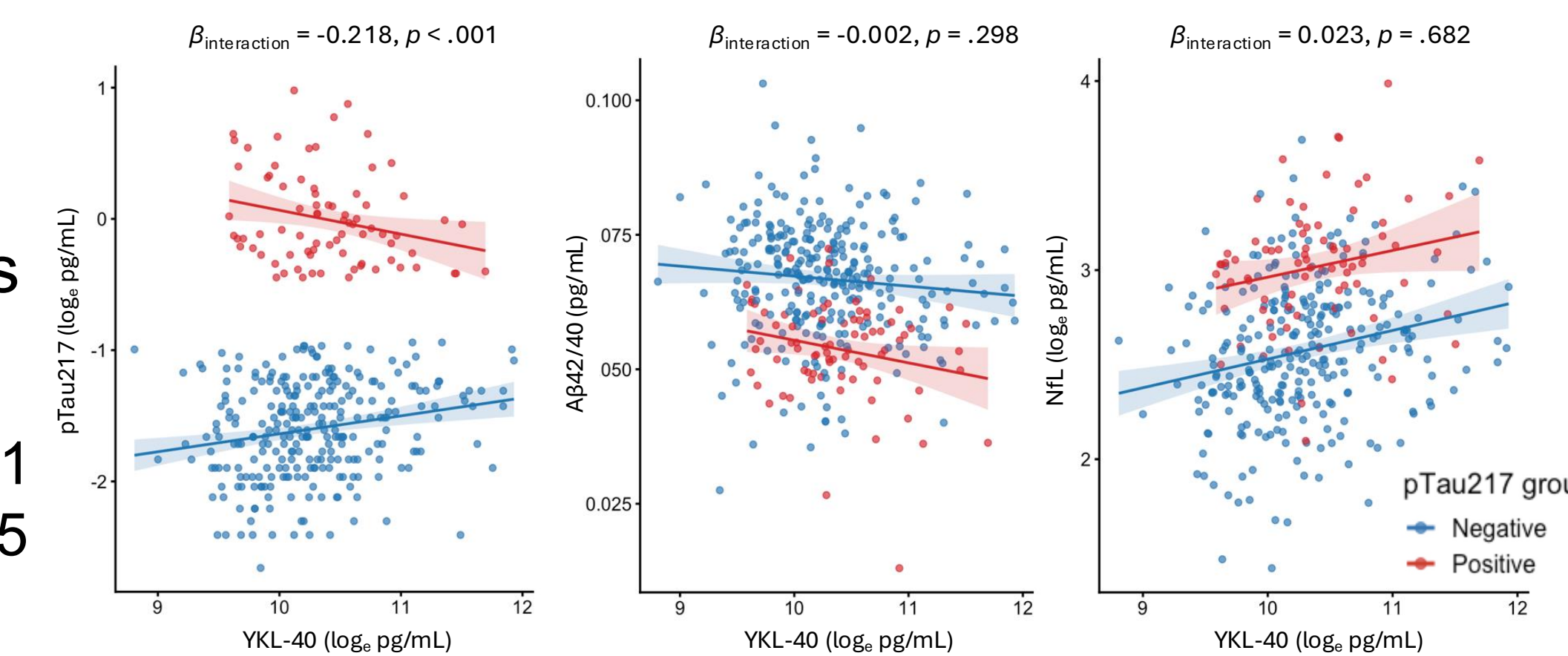


Fig 2. YKL-40 and AD pathology by pTau217 group

- **YKL-40 and A β 42/40** also uncouples with clinical progression (**Fig 3**)
- Stage-dependent effects of YKL-40 is **specific to AD pathology** but not general neurodegeneration (NfL) (**Fig 2**)
- No stage-dependent effects of YKL-40 with neuropsychological outcomes ($p_{\text{interaction}} > .05$)

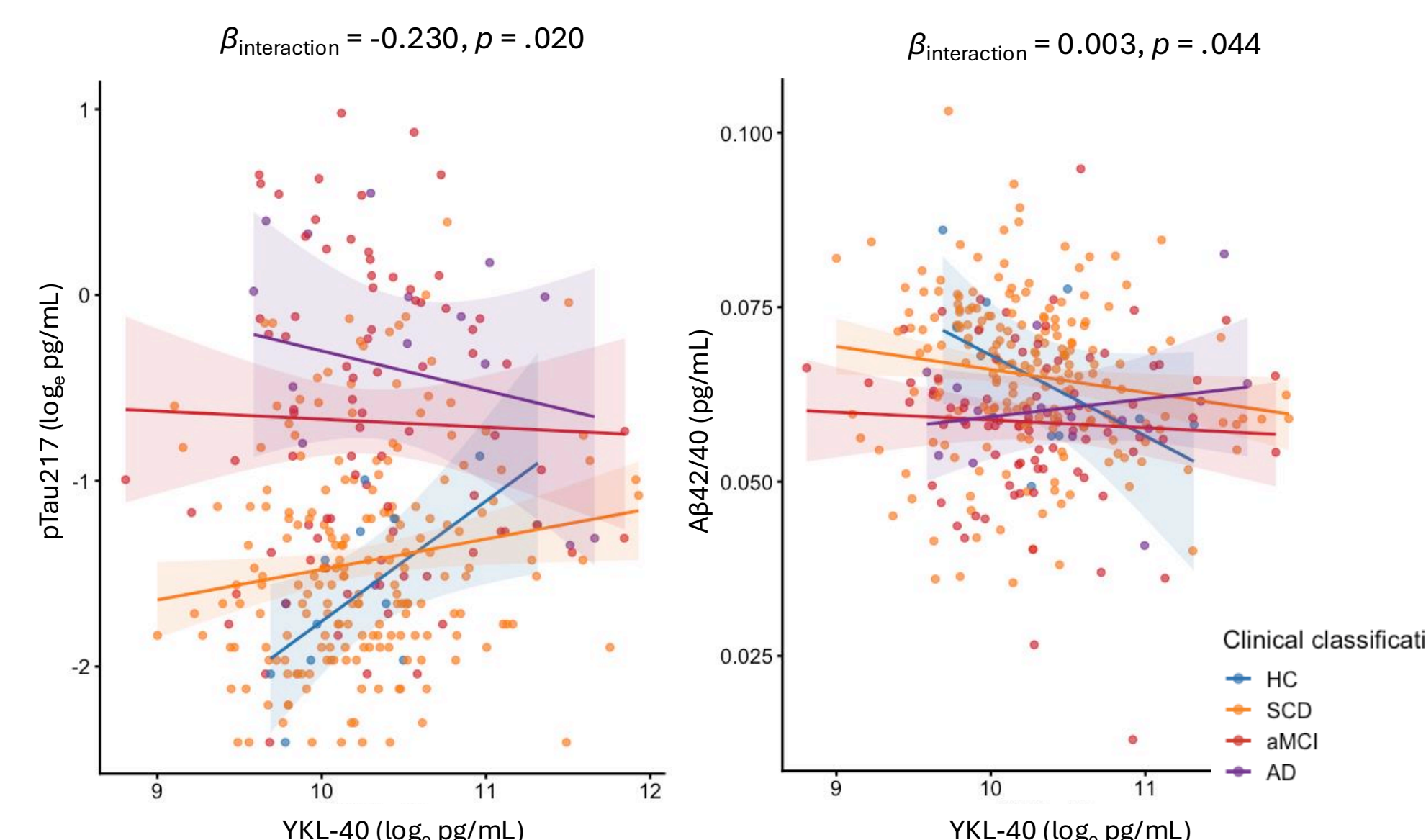


Fig 3. YKL-40 and AD pathology by clinical diagnosis

GFAP showed strong and consistent associations with AD biomarkers, regardless of disease stage (Fig 4)

GFAP showed stronger associations with poorer cognition with increasing clinical severity (Fig 5)

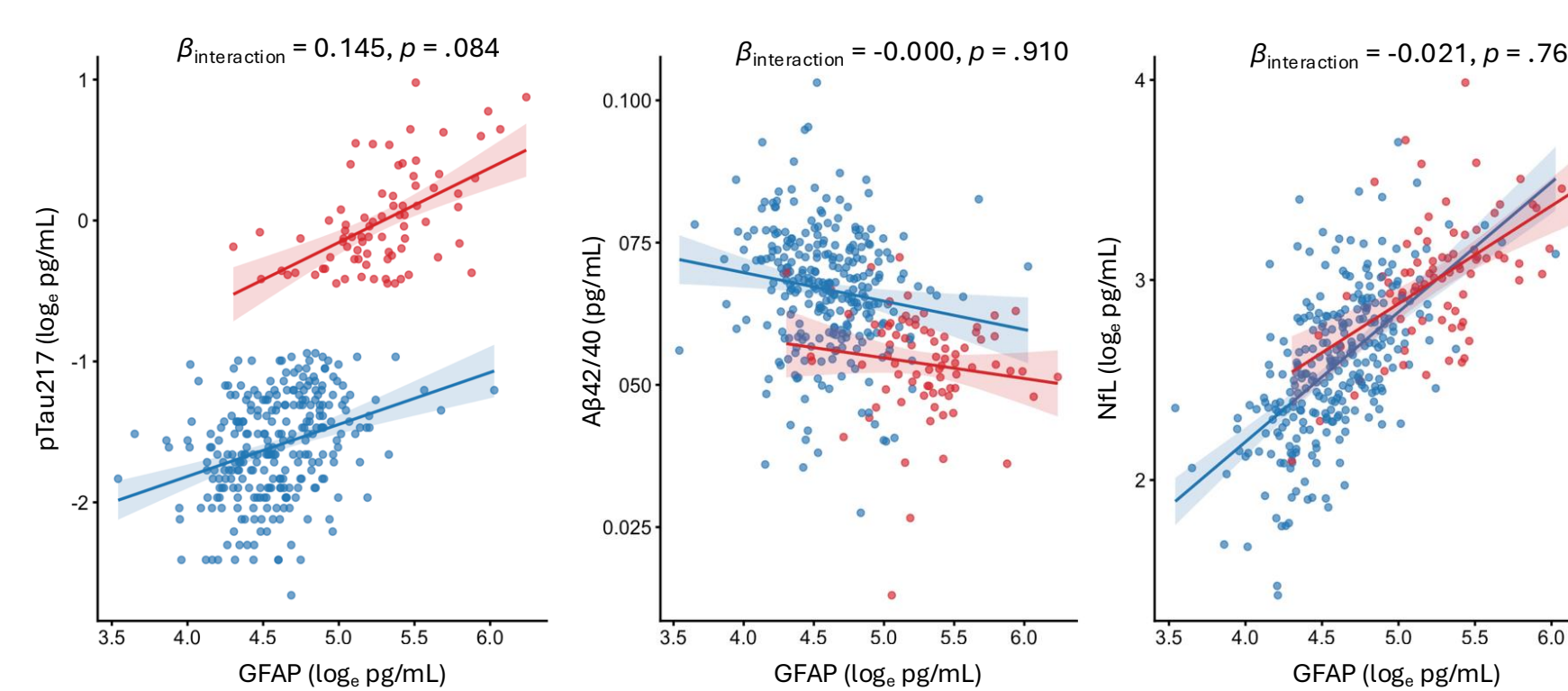


Fig 4. GFAP and AD pathology by pTau217 group

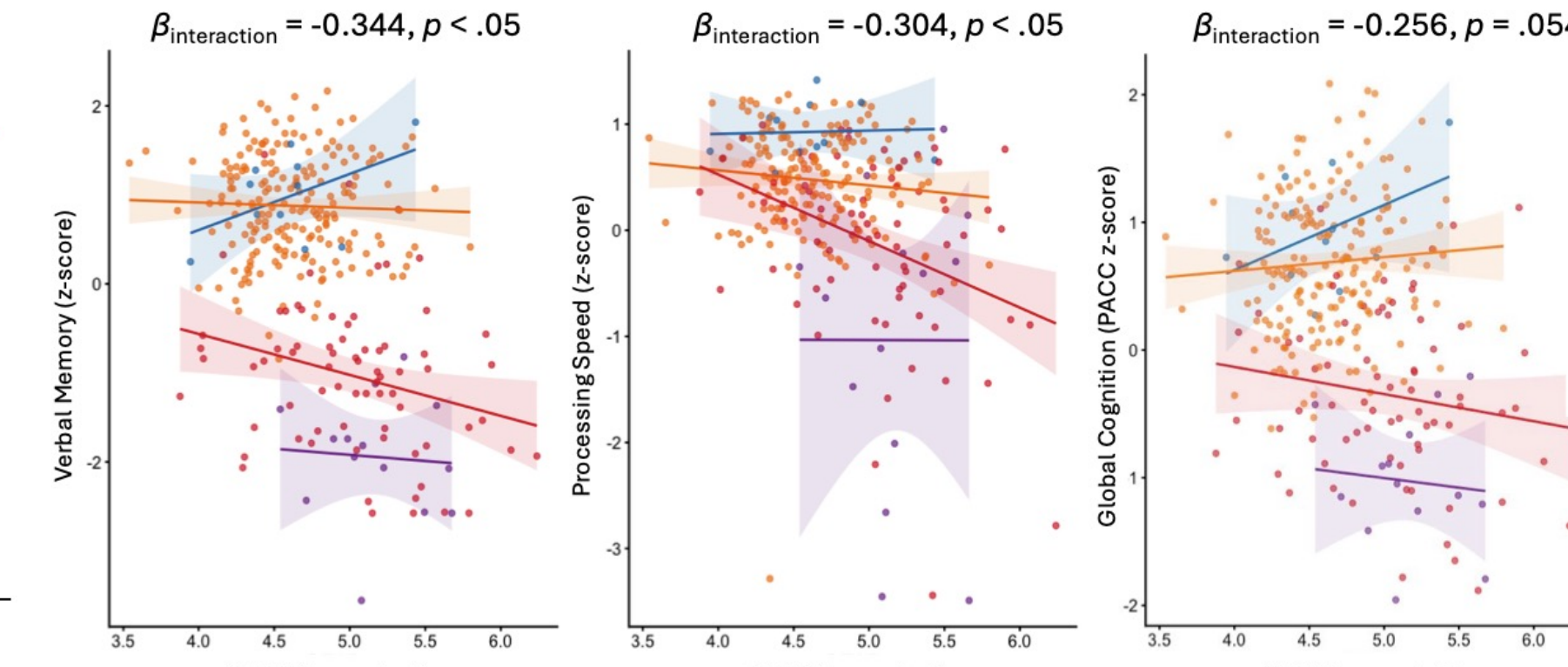


Fig 5. GFAP and cognitive outcomes by clinical diagnosis

CONCLUSIONS

Astrocytic markers GFAP and YKL-40 exhibit **distinct, stage-dependent** relationships with AD pathology and cognition, reflecting **glial dysregulation** with disease progression

- **GFAP** reflects **cumulative structural astrocytic injury** → becomes increasingly clinically relevant as astrocytic injury and neurodegeneration accumulate
- Early rise in **YKL-40** with increasing AD pathology may reflect an **adaptive** astrocytic response to emerging pathological burden → progressive decoupling suggests **saturation** or “**exhaustion**” following chronic glial activation